L.(3) Pharma

د/ أسو

إحنا في المحاضرة السابقة تحدثنا عن الـ Absorption والـ Distribution

هم في هذه المحاضرة هنكمل باقي الـ PharmacoKinetics ــه فاضلها نقطتين
هم الـ Metabolism و الـ Excretion

ونبدأ بالـ

Metabolism = Biotransformation

→ Most drugs will have a prolonged action if terminatn of their action depends only on renal excretion

يعني لو اعتمدنا على الـ excretn فقط ـه الدواء هيبقى الـ effect بتاعه طويل جداً
ـه لكن هناك حاجة بتحصل إسمها Metabol هي اللي بتوقف الـ effect بتاع الدواء
وتساعد على الـ excretn كمان

→ Lipophilic xenobiotics (foreign substances) are transformed or metabolized in our bodies to a more polar substances So, they get more readily excretable

طيب ليه الـ polar هو اللي بيحصله excretn ؟

الإجابة : علشان الـ polar لما يوصل الـ tubules بتاعت الـ Kidney
مش بتقدر يتعملها reabsorptn عن طريق الـ cell membrane
لأنها Polar ولازم علشان حاجة تعدي الـ cell membrane
لازم تبقى Lipophilic زي ما قلنا المحاضرة اللي فاتت في
الحتة بتاعت الـ absorptn اللي فيها الـ ionized والـ non-ion
والـ protonated والـ non-protonated

(*) Metabolic products are often less pharmaco dynamically active than parent drug ; may be even totally inactive as in what happen due to 1st pass effect.

طيب إيه الفرق بين الـ 1st pass eff. والـ Metabolism العادي؟

← الـ 1st pass eff. هو إن الـ drug بيعدي على الـ Liver ويحصله Metabolism قبل ما يوصل الـ systemic circulatn, وبكده بيبقى ملوش أي فايدة خالص

∴ 1st pass effect : it's the Metabolism of drug in the 1st single passage after absorptn, befor reaching the systemic circulatn, ←

← أما الـ Metabolism العادي بيحصل إن الـ drug بعد ما يعدي في الـ systemic circul. ويوصل الـ Body tissue بيعدي على الـ Liver وهناك يحصله Metabolism وبعد كده excretn, وده الطبيعي

(*) Some Metabolic processes may enhance the drug activity or, may reach toxicity.

(*) Enzymes of drug Metabolism have been used in the design of pharmacologically inactive (prodrugs) that are converted to the active molecules in the human body.

(*) Drug Metabolism passes through 2 phases in the human body

وتعالوا نشوف كل phase بيحصل فيها إيه.

Phase I

→ Convert Lipophilic molecules into more polar molecules

ازاى ؟

By introducing or unmasking a polar functional group

eg: $-\overset{+}{N}H_3$ or $-OH$ or $COOH$

ومين اللى بيعمل كده ؟

→ This is catalyzed by the Cytochrome p450 system which is a microsomal mixed function oxidase.

$$\underset{\text{unoxidized}}{\text{Drug}} + O_2 + NADPH + H^+ \xrightarrow{\text{Cyt. p450}} \underset{\substack{\text{oxidized} \\ \text{(polar)}}}{\text{Drug}} + H_2O + NADP$$

→ Cytochrome p450 contain many isoenzymes, Some drugs can induce or inhibit their synthesis

⊛ induced by: ① Carbamazepine ② Phenobarbital ③ Phenytoin ④ Rifampin

⊛ inhibited by: ① Grape fruit Juice ② Azole antifungals ③ Cimetidine ④ Erythromycin

⊛ Drugs Metabolized by Cyp450: ① antihistaminics ② Ketoconazoles ③ anti HIV protease inhibitors

Phenytoin

إيه يا عم إنت كل الأسماء دي؟ هو علينا حفظ؟

الإجابة: إحفظ واحد أو إثنين منهم كل واحدة لأنه الدكتور لم يركز عليها خالص لكن هم موجودين وعلينا.

(*) Also the action of cytochromes p450 is affected by:
1. Drug - drug interactn.
2. non genetic factors eg: race differences.
3. genetic factors eg: individual variance.

(*) Some drugs are eliminated through Cy. p2D6
(But) they aren't common because 50% of clinically used drugs are Cy. p450 substrates.

وحبة كده الشغري.

ودي من محاضرات السنة اللي فاتت.

Cy. P 2 D 6
- 6 → Gene
- D → SubFamily
- 2 → Family

أهم حاجة لازم تعرفها إنه Phase I بيحول الـ nonpolar drugs إلى Polar Subs. عن طريق الـ cytochrom p450 syst.

Phase II

⊛ In this phase → Subsequent conjugation with a more polar endogenous Substrate occur as:
- Sulfuric, gluconic, acetic, amino acids.

More Polar endogenous Substrate

يعني المركب بتاعي بيمسك كمان في حاجة تخليه More, More Polar

⊛ This result in more water Sol. compounds that are therapeutically inactive (totally)

⊛ Glucouronidation is the most common process.

Example for phase I, II on aspirin (acetyl salicylic ā)

COOH, O-COCH$_3$ (non polar) —hydrolysis by cy.p450 (phase I)→ COOH, OH salicylic ā (polar) —+Glucouronic ā→ highly polar comp. to be excreted

بصراحة ماحقتش أنقل المركب ده ولم أجده في أي مصدر ساموني صولو كمان نقله يعني يقول الى ربنا ينزله المحاضرة القادمة

كده إحنا خلصنا ال Metabolism

تعالوا نشوف آخر حاجة في ال pharmacokinetics وهي ال excretion

(*) all drugs pass through phase I then phase II of metabolism

except isoniazide drug (INH) for T.B. treatment.
→ it passes through phase II the phase I of metabolism.

Liver enzymes responsible for metabolism.

* Liver microsomal enzymes (LME)
  or,, Microsomal enzyme system.
  or,, Mixed function oxidases.
  → (Mono oxygenases)

Non microsomal enzyme system

NADPH-cytochrome P450 reductase

$Drug + O_2 \xrightarrow[NADP]{NADPH + H^+} Drug\ (oxidized) + H_2O$

Cytochrome P450
لازم نحفظ ال points بتاعتها كويس اوي

* very important in metabolism

by help of NADP-reductase it can carry out oxidatn,, or,, reductn,, of drugs

* contain many isoenzymes :

Family	Subfamily	Gene
3	A	4
2	C	9
2	D	6

* Most important isoenzyme is cytochrome 3A4 which is responsible for metabolism of 50% of drugs.
* some drugs can induce these enzymes : ------- من المحاضرة
* " " " inhibit " " : ------- " "
* They are affected by : Genetic, non Genetic factors, Drug-drug interactn,,
* Drugs metabolized by cyt. P450 are : ---------- من المحاضرة

Excretion

⊛ The Kidney is the most important excretory organ for drugs & their metabolites.

⊛ Substances excreted in feaces are :
- ⓐ unabsorbed orally ingested drugs
- or ⓑ drug metabolites coming out in bile or secreted directly in intestinal tract, not reabsorbed.

⊛ Renal excretion involves 3 distinct processes :

① glomerular Filteration : Most drugs- unless bound to plasma proteins → pass the glomerular filter Freely.

② Active proximal tubular Secretion : Many drugs as weak à, weak bases are actively secreted in the renal tubule, thus more rapidly excreted.

③ Passive distal tubular reabsorption : ⊛ As drug moves towards distal tubule it's conc. increases, exceeds that of the perivascular space.

∴ Lipid sol. (unionized) drugs passively reabsorbed by diffusion across the tubular membrane → so not excreted in urine.

→ Because of pH partition, weak à are more excreted in Alkaline urine, Vice versa

وده الكلام اللي قلناه المحاضرة السابقة
في المساليت إللي طلناهم بنوع الـ aspirin.

(*) Several important drugs are removed by renal excretion and are liable to cause toxicity in elderly people (Geriatrics), patients with renal diseases.

يعني الـ elimination بتاع الـ drug مهم الـ Kidney بطريقة حسابية (Quantitative)

Quantitative aspects of Renal elimination

ومعلش الحتة دي فيها Math كتير كلمتي الأمر هنطلع منها بحاجة مفيدة في الـ Pharma

Clearance : → plasma clearance is the volume of plasma from which all the drug appears to be removed in a given time (min) expressed as ml / min.

(*) Excretion rate = clearance x plasma conc
mg / min = ml / min x mg / ml

→ when clearance is constant → Excretion rate ∝ plasma conc.

(*) total clearance of drug by several organs is additive
∴ $Cl_{total} = Cl_{hepatic} + Cl_{renal} + Cl_{pulmonary} + Cl_{others}$.

{But} It's impossible for us to measure, add these individual clearance to get the total clearance.

طب هنجيبها إزاي ؟

→ Total clearance can be derived from the steady state equation :

$$Cl_{total} = K_{el} \cdot V_d$$

* Excretion Rate (mg/min) = Clearance (ml/min) × plasma Conc. (mg/ml)

by steady state eq. * $Cl_{Total\ ss} = K_{el} \cdot V_d$ → Vd. of distributn

K_{el} ↓ elimination Rate Const. (clearance Const.

⇒ $K_{el} = \frac{Cl_{Total}}{V_d}$

∴ most Drugs follow 1st order kinetics. as elimination Rate Const. ∝ drug Conc.

* ∴ $C_t = C_0 - \exp^{-K_{el} t}$

$\ln C_t = \ln C_0 - K_{el} t$ at $t_{\frac{1}{2}}$ → $C_t = \frac{1}{2} C_0$

∴ $\ln \frac{C_0}{2} = \ln C_0 - K_{el} t_{\frac{1}{2}}$

$\ln \frac{C_0}{2} - \ln C_0 = - K_{el} t_{\frac{1}{2}}$

$\ln \frac{C_0}{C_0 \times 2} = - K_{el} t_{\frac{1}{2}}$

$\ln \frac{1}{2} = - K_{el} t_{\frac{1}{2}}$

$\ln 2 = K_{el} t_{\frac{1}{2}}$

∴ $t_{\frac{1}{2}} = \frac{\ln 2}{K_{el}} = \frac{0.693}{K_{el}} = \frac{0.693}{\frac{Cl_{Total}}{V_d}} = \frac{0.693 \cdot V_d}{Cl_{Total}}$

∴ $t_{\frac{1}{2}} = \frac{0.693 V_d}{Cl_{Total}}$

$t_{\frac{1}{2}} \propto V_d$

$t_{\frac{1}{2}} \propto \frac{1}{Cl_{Total}}$

(*) Several important drugs are removed by renal excretion and are liable to cause toxicity in elderly people (Geriatrics), patients with renal diseases.

يعني ال eliminatn بتاع ال drug مع ال kidney بطريقة حسابية (Quantitative)

Quantitative aspects of Renal elimination

ومعانى الحتة دى فيها Math كتير كلمتى الأخر هنطلع منها بحاجة مهمة فى ال Pharma

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طيب هنجيبها إزاى ؟

→ Total clearance can be derived from the steady state equation :

$$Cl_{total} = K_{el} \cdot V_d$$

where : cl_{total} → total clearance , V_d → volume of distributn , K_d → constant of clearance (eliminatn rate const.)

طيب إحنا لو جبنا ال K_d بطريقة ما ، وعندنا ال V_d هنقدر نجيب ال cl_{total}

هو دلوقتي إحنا عايزين نجيب ال K_d

(*) Most drugs exhibit 1st order Kinetics where the rate of eliminatn is ∝ to drug conc.

↓ taking this fact exponentially

$$C_t = C_0 \cdot exp^{-Kt}$$

where : C_0 → initial conc of drug in plasma
C_t → conc. after eliminatn of same drug after time (t)

Plotting ($\log C_t$) against (t) → we get a straight line whose slope is ($-K_d$)

→ So we can easily calculate cl_{total} → knowing V_d

$\log C_t$
16
4
2
1 2 3 4 5 6 7 8 9 time
slope = ($-K_d$)
$t_{1/2}$

كده يا شباب إحنا عرفنا نحسب ال cl_{total} وعرفنا نجيب ال $t_{1/2}$ من ال graph

هو عايزين طريقة نحسب بيها ال $t_{1/2}$ بطريقة Mathematically

From the equation $C_t = C_0 \times exp^{-K_d t}$ → ①

→ taking Ln → $Ln C_t = Ln C_0 - K_d t$ → ②

→ at $t_{1/2}$ → $C_t = \frac{1}{2} C_0$ → ③

∴ By substituting from ③ in ②

∴ $Ln \frac{1}{2} C_0 = ln C_0 - K_d t_{1/2}$

∴ $Ln \frac{C_0}{2} - ln C_0 = - K_d t_{1/2}$

∴ $ln \frac{C_0}{C_0 \times 2} = - K_d t_{1/2}$

∴ $ln\ 0.5 = - K_d t_{1/2}$ ∴ $Ln\ 2 = K_d t_{1/2}$

∴ $t_{1/2} = \frac{Ln\ 2}{K_d} = \boxed{\frac{0.693}{K_d}} = \frac{0.693}{\frac{Cl_{total}}{Vd}} = \boxed{\frac{0.693\ Vd}{Cl_{total}}}$

$t_{1/2}$ → the half life of the drug i.e. → is the time taken for C_t to decrease by 50%

$t_{1/2}$ → is inversly related to the clearance, directly prop. to the volume of distribution of the drug.

∴ the half life of a drug is increased by ∴

① ↓ clearance ∴
- ⓐ ↓ renal plasma flow
- ⓑ renal disease.
- ⓒ ↓ metabolism by enzyme inhibition.
- ⓓ Liver disease.

② ↑ $\bar{V}_d$ by another drug displacement.

كده أظن بان الحوار سهل وبسيط

ده هناك قانون أخير في كده لوحده نتزفه وخلاص

$$CL_{drug} = \underset{\text{(blood flow)}}{Q} \times \underset{\text{(extraction ratio)}}{E}$$

$$= Q \times \left[\frac{C_A - C_{\bar{V}}}{C_A}\right]$$

where C_A → arterial end drug conc.
$C_{\bar{V}}$ → Vein end drug conc.

$$Cl_{Drug} = Q_{\text{Blood flow}} \times E_{\text{Extraction Ratio}}$$

$$= Q \left[\frac{C_A - C_V}{C_A} \right]$$

C_A → Drug conc. in artery

C_V → " " " vien-

∴ the half life of a drug is increased by :

① ↓ clearance : ⓐ ↓ renal plasma flow
ⓑ renal disease.
ⓒ ↓ metabolism by enzyme inhibition.
ⓓ Liver disease.

② ↑ Vd by another drug displacement.

كده أظن بان الحوار سهل وبسيط

ه هناك قانون آخر من كده لوحده ونحفظه وخلاص

$$CL_{drug} = Q \text{ (blood flow)} \times E \text{ (extraction ratio)}$$

$$= Q \times \left[\frac{C_A - C_V}{C_A} \right]$$

where C_A → arterial end drug conc.
C_V → Vein end drug conc.

ومع آخر حتة في ال   أنا اسم نفسي من قاع الصفحة

Pharmakokinetics دي سيدنا أسال وأحيها تاني

→ a 2 compartment model is often needed. in this Case the Kinetics is biexponential.

→ The 2 components roughly represents the processes of transfer between plasma & tissues [α. phase] and elimination from plasma [B - phase]

oral dose → ○

absorption K_{abs}

I.V dose → Central compartment

K_1 → Peripheral Compart. (body tissues)

← K_2

K_d → excretion

$K_{metabolism}$ → metabolism

① is distribution phase

② is elimination phase

Serum conc. vs (Time); $C_0 = 1$; $t_{1/2}$

extrapolation to time (zero) give C_0 → the hypothetical drug conc. predicted if the distribution had been achieved instantly

rapid injection of drug

The Human Nervous System

CNS (central nervous syst.)
→ Brain & spinal cord

(Peripheral nervous syst.) **PNS**
→ neurons & ganglia outside Brain, spinal cord

Efferent (motor) neurons
Output
اللي خارج من CNS

Afferent (sensory) neurons
input
اللي داخل

Somatic N.S. (Voluntary)

Autonomic N.S. (Involuntary)
هو ده اللي احنا هنشرحه بالتفصيل

- Enteric
- Sympathetic
- Parasympathetic

(*) → Beside Nervous system → Endocrine system helps in Body Control ie,, regulatn,, of homeostasis.

(*) → A.N.S (autonomic N.S) works by **Neurohormonal theory**

Definition:

"it's the transmission of nerve impulse across a synapse by secretn,, of a chemical neurotransmitter."

(*) → A.N.S is faster in homeostasis regulatn,, than Endocrine system as it acts on Both ganglionic synapse & organ synapse

يا عم إنت عمال تقول لنا synapse ← ممكن تفكرنا بيه ؟

→ Synapse is the Junctn,, between any 2 neurons or,, between a neuron & target organ

organ

ganglionic synapse (bet. 2 neurons)

organ synapse (bet. neuron & organ)

Role of C.N.S in A.N.S Activity

(*) Although the A.N.S is a motor system, it requires a sensory input from peripheral structures to provide information on the state of affairs in the body.

إيه الفرق ده؟

← لازم الـ A.N.S يجيله sensory input ← فايدته إنه يقول للـ A.N.S حالة الجسم و الـ A.N.S أخذ المعلومات ده و يبتدي يشتغل بحيث إنه يضبط الجسم

(*) These afferent (sensory) impulses originates from the Viscera, other organs then travel to integrating centres in the C.N.S as medulla oblongata, spinal cord, hypothalamus

(*) These centres respond to stimuli by sending out efferent (motor) impulses via the A.N.S.

(*) Emotions Can modify the activity of A.N.S

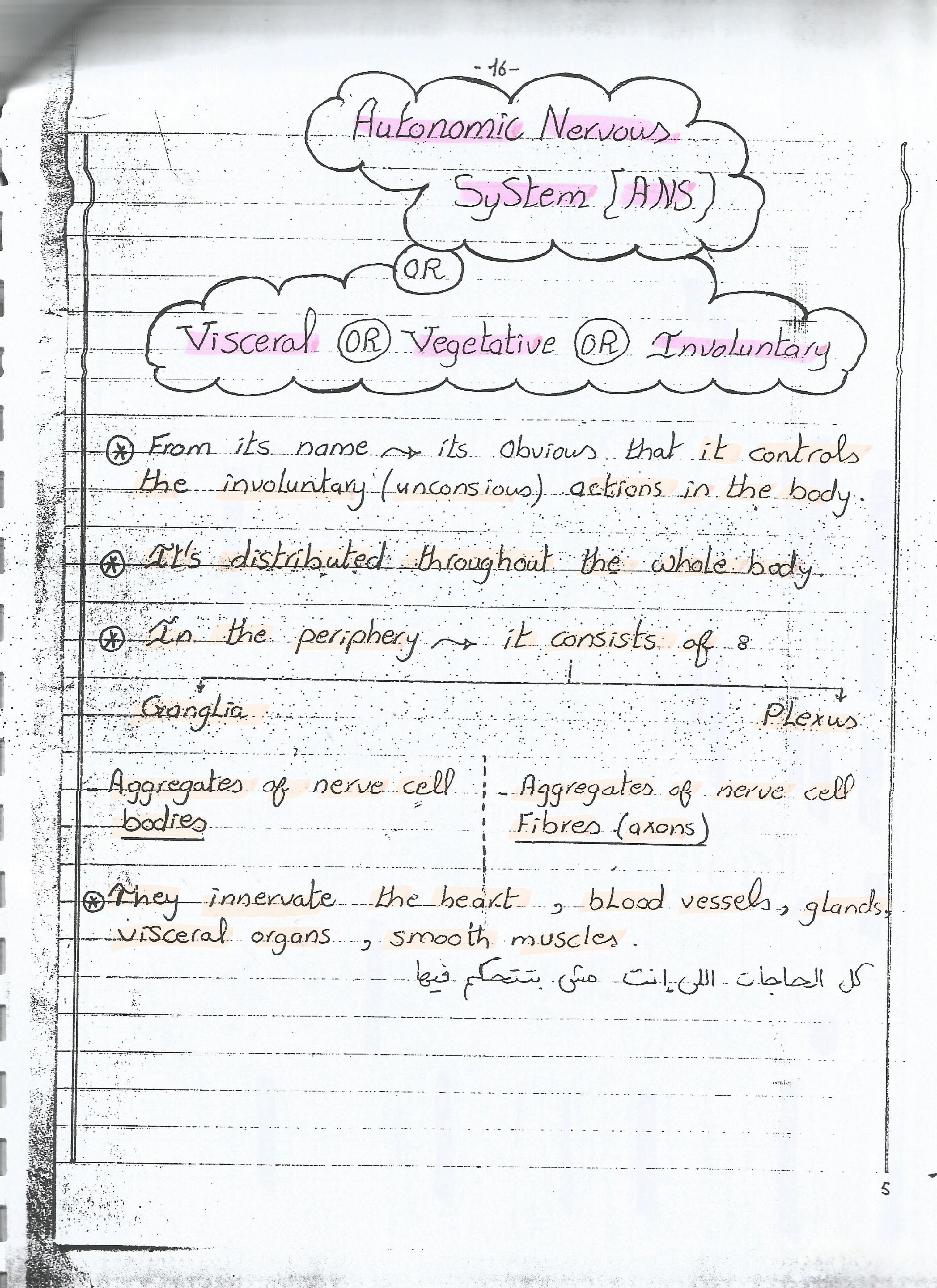
fear — pleasure — rage

فهمت بقا ← علاقة الـ C.N.S بالـ A.N.S

(*) Reflex arcs (actions) → occurs in ganglia that are entirely outside the cerebrospinal axis for very rapid actions that doesn't need thinking or human consciousness at all.

كل الكلام اللى فات ده قديم ومعروف

← تعالوا بقا نركز شوية على الـ A.N.S وندرس تفاصيله.



Autonomic Nervous System [ANS]

OR

Visceral (OR) Vegetative (OR) Involuntary

(*) From its name → its obvious that it controls the involuntary (unconsious) actions in the body.

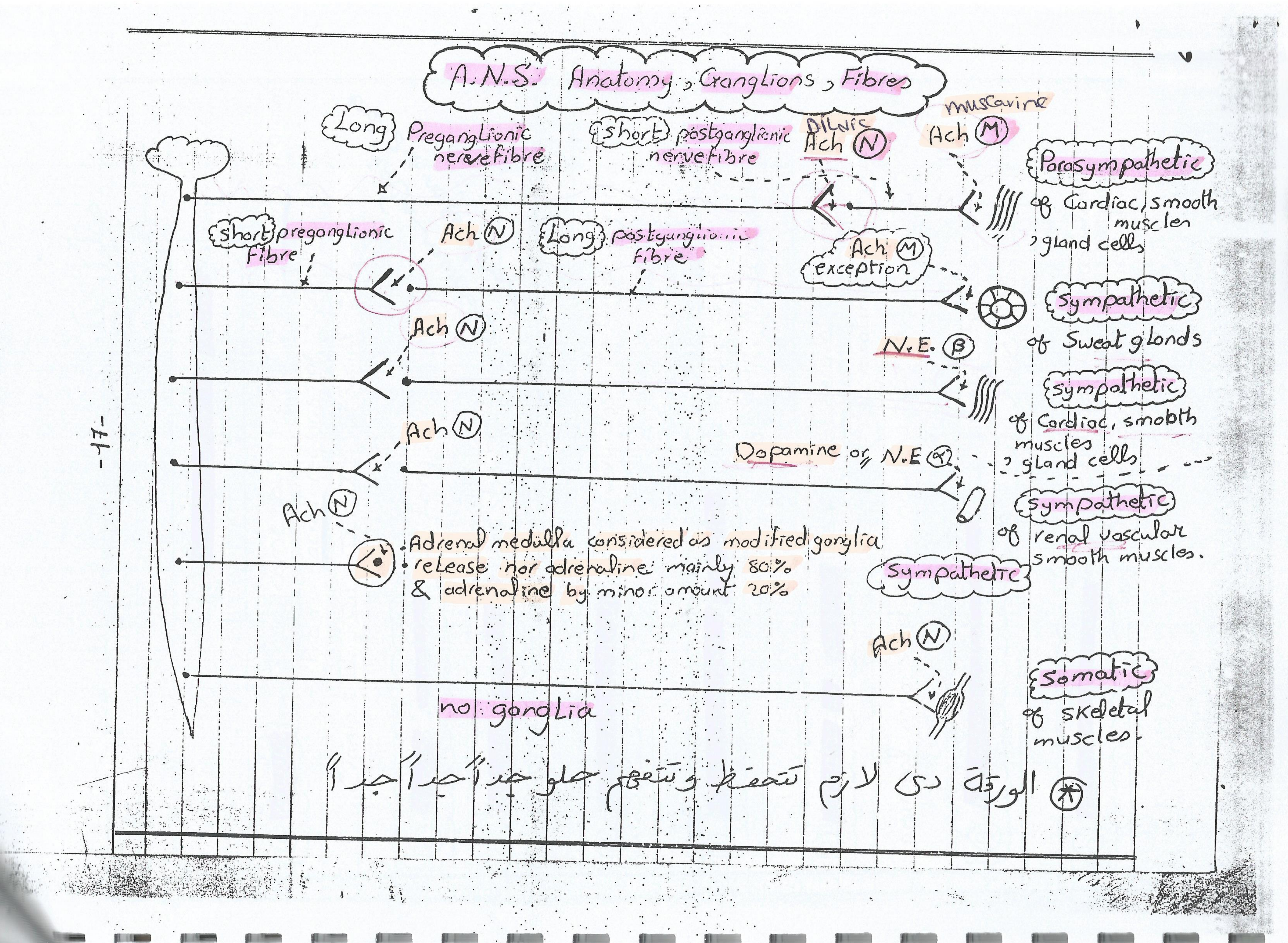
(*) It's distributed throughout the whole body.

(*) In the periphery → it consists of :

Ganglia	Plexus
- Aggregates of nerve cell <u>bodies</u>	- Aggregates of nerve cell <u>Fibres (axons)</u>

(*) They innervate the heart , blood vessels , glands , visceral organs , smooth muscles .

كل الحاجات اللي انت مش بتتحكم فيها


A.N.S. Anatomy, Ganglions, Fibres
Long Preganglionic nerve fibre
Short postganglionic nerve fibre
Nicotinic
Ach (N)
muscarine
Ach (M)
Parasympathetic
of Cardiac, smooth muscles
, gland cells
Short preganglionic Fibre
Ach (N)
Long postganglionic fibre
Ach (M)
exception
Sympathetic
of Sweat glands
Ach (N)
N.E. (β)
Sympathetic
of Cardiac, smooth muscles
, gland cells
Ach (N)
Dopamine or N.E (α)
Sympathetic
of renal vascular smooth muscles.
Ach (N)
• Adrenal medulla considered as modified ganglia
• release nor adrenaline mainly 80%
& adrenaline by minor amount 20%
Sympathetic
Ach (N)
Somatic
of skeletal muscles.
no ganglia
-17-
الورقة دي لازم تتحفظ وتتفهم حلو جداً جداً

ومحلش هطول عليكم وهاشرح الرسمة اللى فاتت حتة حتة

① Parasympathetic neurons.

ⓐ origin → They come out from the Cronium in brain, from sacral regions of spinal cord.

Cranio : III , VII , IX , X , Sacral : $S_{2,3,4}$

Cronium → Brain
Sacral region → S. Cord

ⓑ Pregang. nerve fibre → Long

ⓒ Postgang nerve fibres → short

ⓓ Ganglion position → very close to target organ

ⓔ Neurotransmitter at ganglion → Acetylcholine
or // dil. Nicotine

ⓕ receptor at ganglion → cholinergic neuronal
or // (N) → nicotinic neuronal

neuronal means between neuron, neuron.

ⓖ Neurotransmitter at organ → Acetyl choline
or // Muscarine

ⓗ receptor at organ → cholinergic musculine
or // (M) Muscarinic musculine

7

② Sympathetic neurons

ⓐ origin → They come out of thoraco-lumbar regions of the spinal cord (from $T_1 \rightarrow L_3$)

ⓑ Pregang. nerve fibres → short

ⓒ Postgang. nerve fibres → Long.

Thoracic lumber

ⓓ Ganglion position → close to C.N.S.

ⓔ Neurotransmitter at ganglion → Acetylcholine or// dil. Nicotine

ⓕ receptor at ganglion → Cholinergic neuronal or// (N) nicotinic

ⓖ Neurotransmitter at organ → Generally it's N.E. (norepinephrine)

, in case of renal vascular smooth muscles can be also dopamine beside N.E.

exception → at sweat gland → Acetylcholine is produced instead of N.E.

ⓗ receptor at organ → Adrenergic → β, → α

كل ال Points اللى فاتت معكم تبقى Comparison
بين ال symp. وال parasymp.

③ Somatic neurons

* it differs from A.N.S. in that → it consists of 1 neuron coming out of the spinal cord, goes directly to target organ (skeletal muscles) with no ganglia in the middle

* Neurotransmitter at organ → Acetylcholine
  or,, dil Nicotine

* receptors at organ → cholinergic musculine
  or,, Nicotinic musculine

N.B. → The denervated skeletal muscle Lacking Myogenic tone are paralyzed & atrophied
يعنى لو شلت skeletal muscle و شلت منها ال nerve supply
هيحصلها شلل وتموت

But smooth muscles, glands generally retain some Level of spontaneous activity independant of intact innervation.
لكن ده مش بيحصل فى حالة smooth mus. أو glands

(4) Enteric Nerous system

(*) Although E.N.S is classified as a third division of the A.N.S., it's actually composed of components of sympathetic & Parasympathetic nervous systems , has a sensory nerve connectn.

(*) It controls the processes of mixing, propulsion, absorptn of nutrients in the GIT.

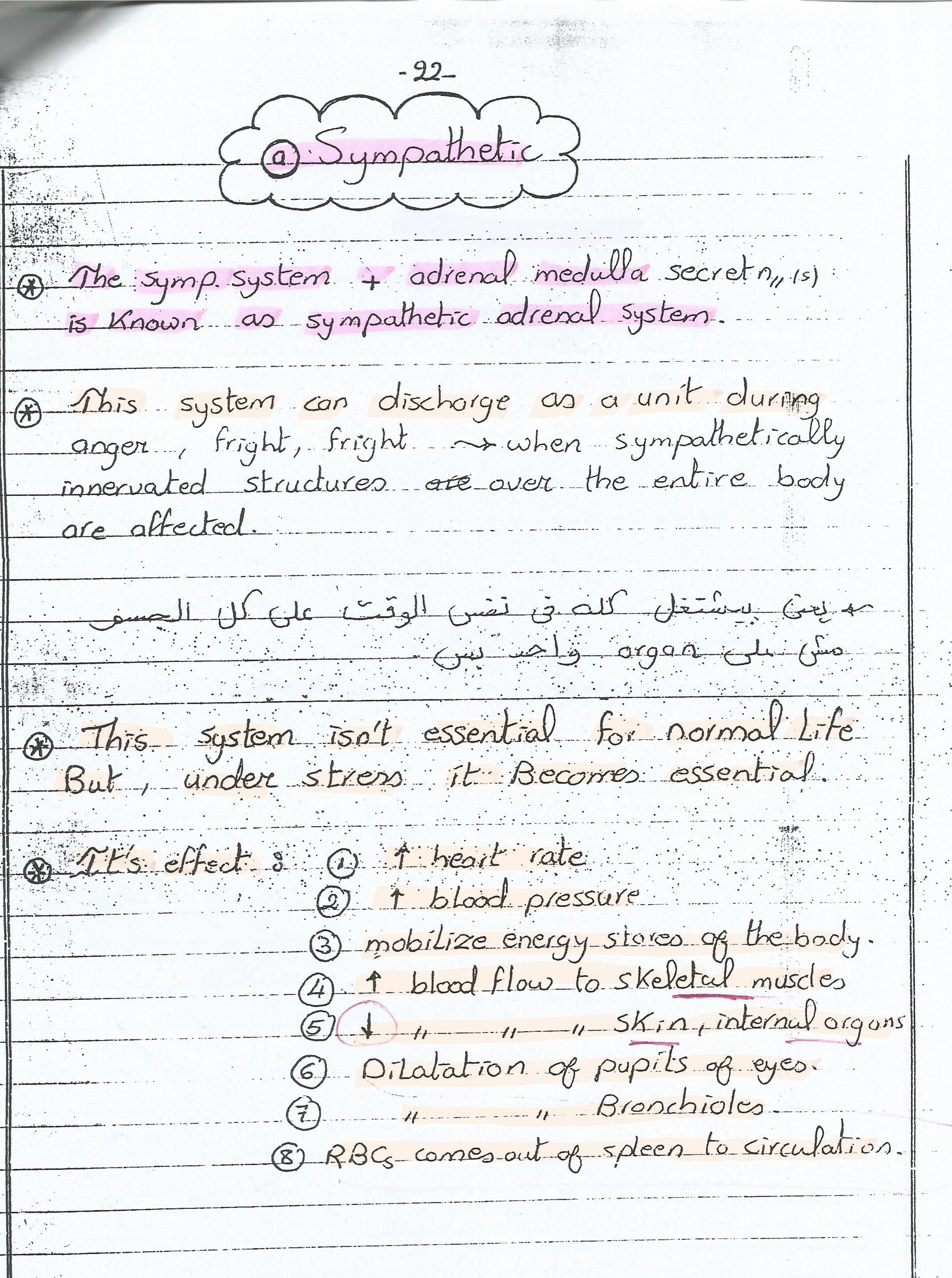
كده احنا خلصنا ال anatomy of A.N.S
وال Ganglia وال Neurotransmitters

ـــه تعالوا بقى كده نشوف مع بعض
ال

Physiology of the A.N.S

Sympathetic | Parasympathetic

They regulate the activities of the structures that Functions below the Level of Consciousness



(a) Sympathetic

* The symp. system + adrenal medulla secretn. (s) is known as sympathetic adrenal system.

* This system can discharge as a unit during anger, fright, fright → when sympathetically innervated structures ~~are~~ over the entire body are affected.

→ يعني بيشتغل كله في نفس الوقت على كل الجسم مش على organ واحد بس

* This system isn't essential for normal life But, under stress it Becomes essential.

* It's effect :
  1. ↑ heart rate
  2. ↑ blood pressure
  3. mobilize energy stores of the body.
  4. ↑ blood flow to skeletal muscles
  5. ↓ " — " — " skin, internal organs
  6. Dilatation of pupils of eyes.
  7. " — " Bronchioles.
  8. RBCs comes out of spleen to circulation.

(b) Parasympathetic

* Parasympathetic system is organized mainly for discrete [individually distinct] & Localized discharge. ie,, never discharge as one unit.

→ if it acts as one unit → undesirable symptoms are produced.

← يعني ممكن يشتغل على organ و ميشتغلش على organ تاني

مش زي الـ symp. sys. ده لما بيشتغل ← بيشتغل على الجسم كله مرة واحدة..

* It's required & essential for Life ie,, for digestive processes, eliminatn,, of wastes, conservation of energy, maintenance of organ function during periods of minimum activity.

* It's Known as Rest & Digest system.

* It's effect :
  1. Lowers heart rate
  2. ↓ blood pressure
  3. ↑ Gastrointestinal movement, secretn,, , absorptn,,.
  4. protects Retina of eye from xss Light
  5. empties the urinary bladder & rectum.

(*) → Important to know that in sympathetic, parasympathetic actions → there's a kind of physiological antagonism
يعنى ال effect بتاعهم عكس بعض

except in :

① Salivary glands → Parasym. → ↑ secretn. → watery (profuse)
→ Sym. → " " → viscid (sparse)

② Atrial conductivity from S.A. node of heart to A.V node → Parasymp. → ↑↑ atrial conduct.
→ Symp. → ↑↑ " " .
تعالوا لو مش فاهمينها وأنا أشرحها لكم

③ Male genitalia → Parasym → erection
→ Symp. → ejaculatn.

Page (24) → Parasympathetic innervatn. only as constrictor (circular) pupile muscles

iris
pupil
those are the circular muscles

→ small blood vessels that contain non innervated Muscarinic receptors
يعنى إيه ؟
يعنى ال B.Vs عليها Muscarinic receptors لكن مش جاى لها neuron من ال A.N.S.
لكن أنا لو اديت دواء هيوصل ل ال receptor عادى جداً ويشتغل كأنه جاله impulse من ال parasympathetic system.

* الحتة دى مهمة جداً جداً ولازم تكون عارفها.

→ we said that M_2, M_4 work by G_i receptor of cAMP system.

→ add to them α_2 adrinergic receptor → it works in the same inhibitory mechanism.

→ we said that G_s receptor works by increasing cAMP But we gave no examples

examples : adrinergic β_1, β_2, β_3 receptors

→ we said that M_1, M_3, M_5 work by G_p → of Phosphatidyl inositol diphosphate system

→ add to them α_1 adrinergic receptor.

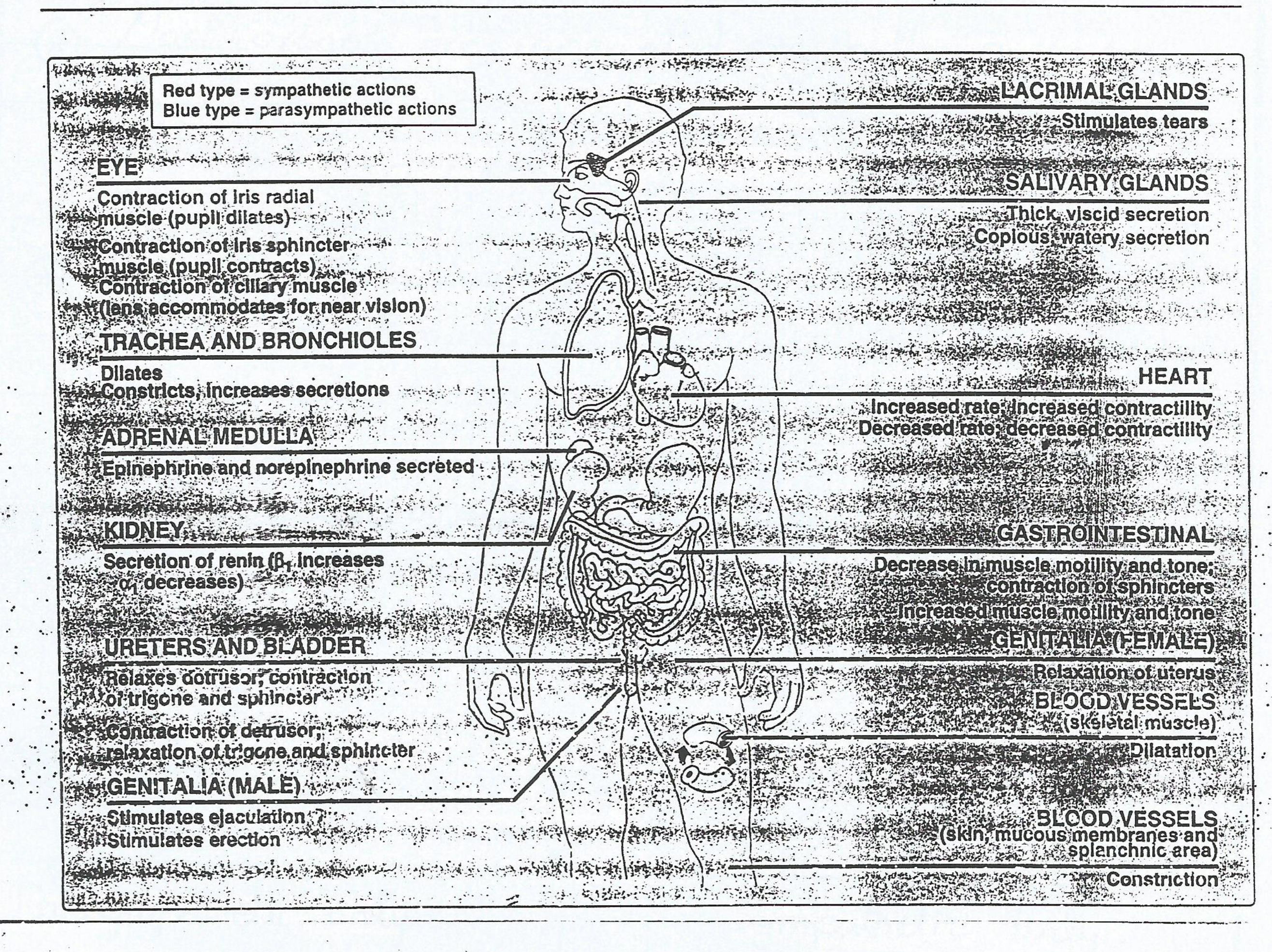
وعلشان نلم كل أنواع الـ receptors هنرسم الرسمة دى

Ion channels — N_n, m — Na^+ ↓ depolarization, K^+ ↑ hyperpolarization; activation or inhibition

G protein coupled receptors:

- $\beta_{1,2,3}$ — Gs — ⊕ A.C. — ATP → cAMP
- α_2, M_2, M_4 — GI — ⊖ A.C.
- α_1, M_1, M_3, M_5 — Gp — ⊕ PLC — PIP_2 → IP_3, DAG — ↑ Ca^{+2}, phosphorylation of proteins

الـ sympathetic دائما هو الـ effect الأول
الـ Parasymp. " " " " الثاني



Dual innervation

(*) Most organs are innervated by both parts of A.N.S → Symp → (↑) heart rate. } مثلا يعني
→ Parasymp → (↓) " " .

(*) Despite the dual innervation → one system usually predominates in controlling the activity of a given organ.

for example:

in heart → the vagus nerve is the Predominant factor for controlling the rate.

(*) only few organs receive only one kind of innervation

Parasympathetic only	Sympathetic only
as constrictor pupile Muscles (circular Muscles)	as - Dilator pupile Ms. (Radial Ms)
	- ventricles of heart.
	- Adrenal medulla
, small Blood vessels contain non innervated Muscarinic receptors.	- Sweat gland
	- Kidney

* Neuro Transmitter Receptor *

Ion-channel Coupled R

- R + Drug (N.T) Binding →
  ± Polarizing state → Depolarizing →
  Rest → hyperpolarizatn

* Any sub ↓ +ve outside
  ↓ -ve inside
  or ↑ -ve outside
  ↑ +ve inside
  (depolarizatn)
  } excitatory Agent

* " " ↑ +ve outside
  ↑ -ve inside
  (hyperpolarizatn)
  } inhibitory Agent

*** Cholinergic Nicotinic Receptors**

G-protein Coupled R

R + N.T → 2nd messenger

cAMP system

phosphorylatn of serine & therionine of Protein

↑ cAMP

- ↑ Ca^{++} influx in heart → ↑ Rate
- ↓ kinase enzyme in smooth muscle → relaxant

→ M_2, M_4 Receptors

Phospholipase C-system

acts on Phosphatidyl inositol Diphosphat

- IP_3 → ↑ Ca^{+} from Endoplasmic Reticulum → Contractn
- DAG → Phosphorylat → Cellular response

→ M_1, M_3, M_5 Receptors

*** muscarinic R**

تعالوا نتكلم شوية عن ال receptors ونشوف إيه أنواعها
و ال Mechanism بتاعها بالتفصيل شوية عن المحاضرة الأولى

Neurotransmitter Receptors

Definition :

They are membrane proteins that provide a binding site that recognize and respond to neurotransmitter molecules.

4 Types :

1. ion channel coupled receptor
2. G-protein " "
3. enzyme Linked "
4. receptors inside the cell

→ The most important 2 types to study now to Know the mechanism of cholinergic , Adrinergic receptors are :

- ion channel coupled receptor.
- G-protein " " .

$Na^+ Na^+ Cl^- Cl^- Cl^- Cl^-$ — net -ve charge

Depolarizatn (excited) state — net +ve charge

$K^+ K^+ K^+ Na^+ Na^+ Na^+ Cl^- Cl^- Cl^- Cl^-$

→ this process occurs in milli sec.

→ then the membrane returns to its rest (polarizatn) state by K^+ efflux followed by Na^+ - K^+ pump.

→ The whole process can be represented as a graph (curve) :

+30 mV (depolarizatn)

↑ excitatory Agents

-70 mV

-90 mV polarizatn (rest)

-90 mV

-100 mV hyperpolarizatn

↑ inhibitory Agents

→ From the curve we can conclude :

① any Substance that decreases +ve charge outside or decreases -ve charge inside can lead to depolarizatn
∴ it's considered as excitatory agent.

② any Sub. that increases +ve charge outside (K^+ efflux) or increases -ve charge inside (Cl^- influx) can cause hyperpolarizatn
∴ it's considered as inhibitory agent.

Receptors working using this Mechanism are:

Cholinergic Nicotinic receptors

which are present at: (1) all ganglionic receptors
(2) somatic Neuromuscular Junctn
(3) Synapse at sweat glands of sympathetic innervatn.

والرسمة اللي جابها الدكتور هي دي:

in Case of excitatory input

Ca^{+2}

neurotransmitter discharged in synapse.

Na^+

sodium ions enter inside causing depolarizatn, excitatn of this organ or neuron.

Na^+ (channel open) causing depolarizatn

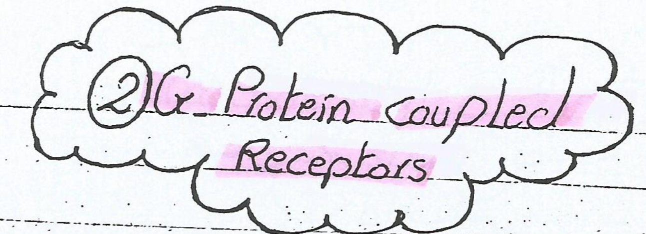
K^+ (efflux)

in Case of inhibitory input

K^+ efflux causes hyper polarizatn, causing inhibition.

كده احنا خلصنا ال ion channel coupled receptor

- تعالوا نشوف النوع التاني وهو ال G protein coupled receptor



* Binding of chemical neurotrans. to receptors activate enzymatic processes within the cell membrane that ultimately result in cellular changes such as phosphorylatn of intracellular proteins.

* Neurotransmitter → Signal
  Receptor → Signal detector & transducer

* "Second messenger" molecules are produced in response to neurotransmitter binding to the receptor, translate the extracellular signal into a response → propagated, amplified within the cell.

* The most widely known second messengers are:
  1. adenylyl cyclase system.
  2. Calcium / phosphatidyl inositol system.

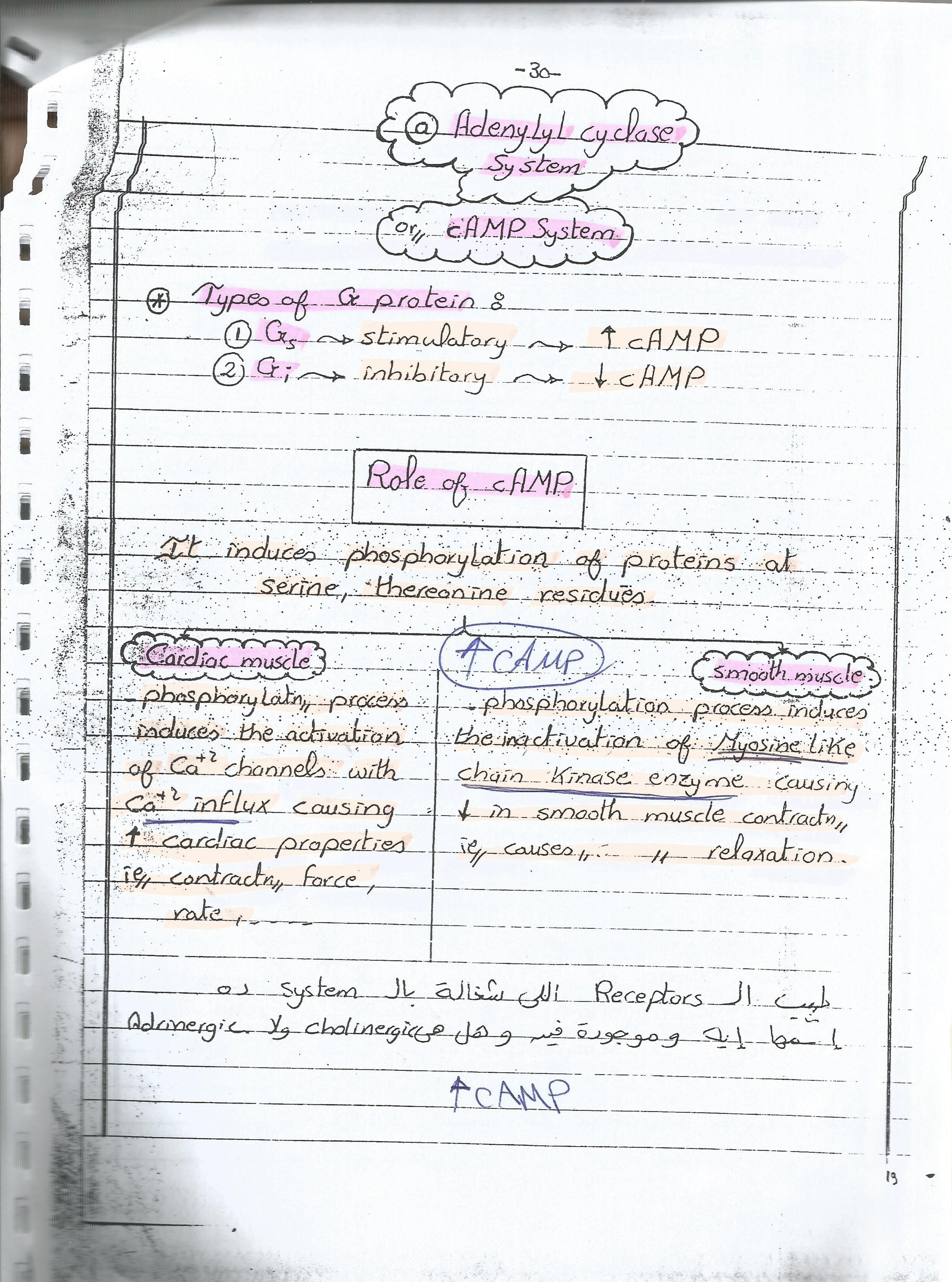
تعالوا نشرح كل system فيهم بيشتغل ازاى

Second messenger

- Adenylyl Cyclase
- Calcium / phosphatidyl

phosphatidyl inositol

Adenylyl Cyclase



ⓐ Adenylyl cyclase System

or, cAMP System

* Types of G protein :
  1. G_s → stimulatory → ↑ cAMP
  2. G_i → inhibitory → ↓ cAMP

Role of cAMP

It induces phosphorylation of proteins at serine, thereonine residues.

↑ cAMP

Cardiac muscle	smooth muscle
- phosphorylatn, process induces the activation of Ca^{+2} channels with Ca^{+2} influx causing ↑ cardiac properties ie, contractn, force, rate, ...	- phosphorylation process induces the inactivation of Myosine like chain Kinase enzyme causing ↓ in smooth muscle contractn, ie, causes " " relaxation.

طيب ال Receptors اللى شغالة بال System ده
اسمها إيه وموجودة فين وهل هى Adrenergic ولا cholinergic

↑ cAMP

* This Kind of receptors working By this Mechanism are :

cholinergic , Muscarinic → Kind M_2 , M_4
present in heart muscle , smooth muscle

إيه حكاية M_2, M_4 دي ؟ يعني إيه الأرقام دي ؟
مش كلها Muscarinic وخلاص ؟

Answer : → No, in mammals there are 5 distinct types of muscarinic receptors
M_1 , M_2 , M_3 , M_4 , M_5

→ M_2 , M_4 → present in Cardiac Muscles , Smooth muscles
work by cAMP system.

↓cAMP

But you have to Know that when agonist bind to these M_2 , M_4 receptors → G_i (inhibitory) is the one which acts → decreasing cAMP causing cardiac muscle relaxatn & smooth muscle contractn.

→ M_1 , M_3 , M_5 work by another system which is Calcium / phosphatidyl inositol system
or Phospholipase C system.

وتعالوا نشوف ال system ده بيشتغل إزاي.

(b) Calcium / Phosphatidyl inositol diphosphate system

or,, Phosphalipase C system

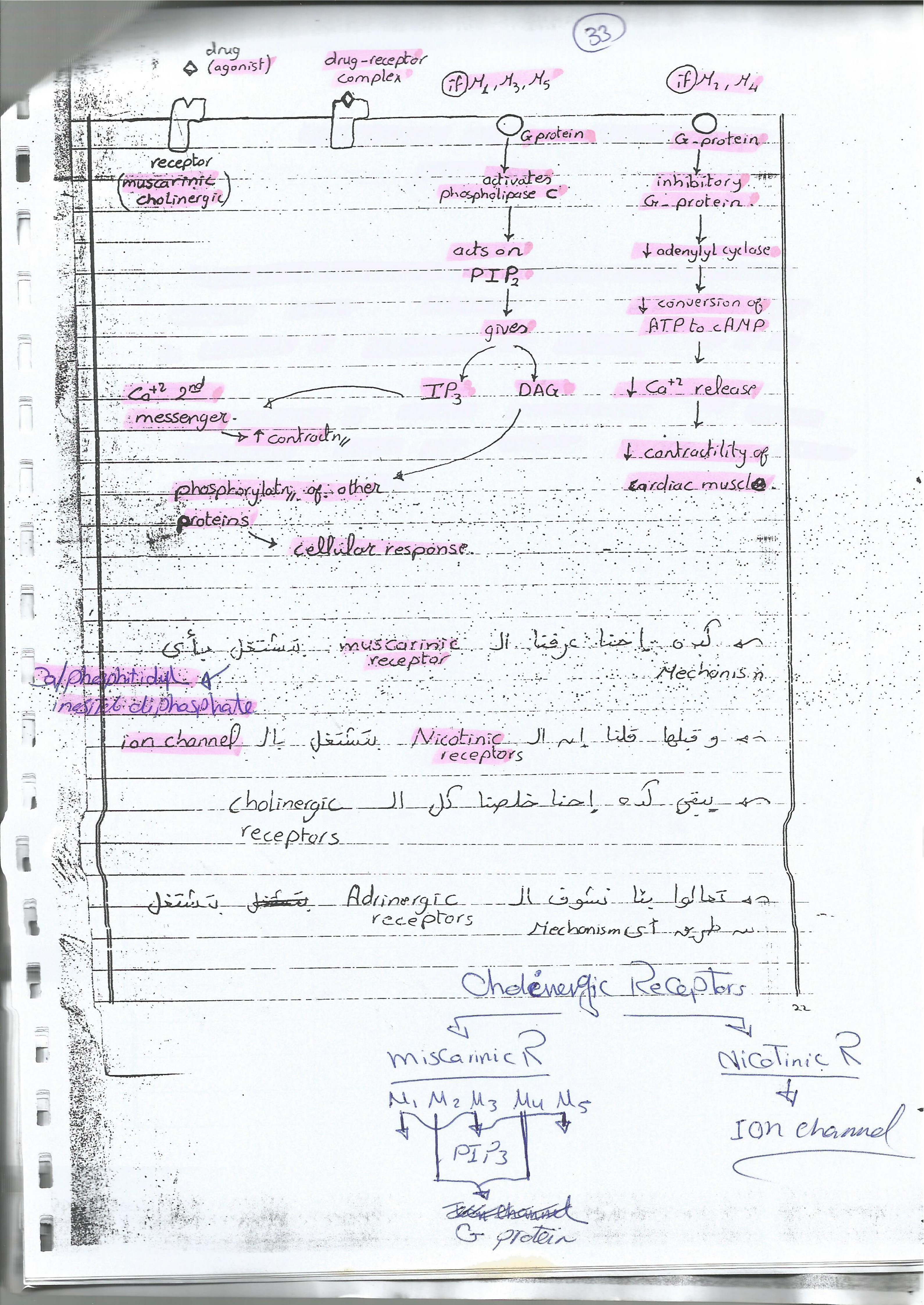
* Binding of Agonist to muscarinic ACH receptors ($mACHR_s$) of type 1, 3, 5 (M_1, M_3, M_5) activates phospholipase C enzyme

* Phosphalipase C enzyme causes hydrolysis of Phosphatidyl inositol 4,5 diphosphate into 8
  1. Diacyl glycerol (DAG)
  2. Inositol triphosphate (IP_3)

* IP_3 causes the release of intracellular Ca^{+2} ions from endoplasmic reticulum causing the action of Ca^{+2} dependant phenomena as muscle contraction.

* DAG activates protein Kinase enzyme causing phosphorylation of numerous proteins Leading to various physiological responses.

وعلشان نلخص ال 2systems اللى فاتوا بنوع ال
muscarinic cholinergic receptors
هنرسم الرسمة اللى جاية دى .


33
drug (agonist)
drug-receptor complex
receptor (muscarinic cholinergic)
if M1, M3, M5
G protein
activates phospholipase C
acts on PIP2
gives
IP3
DAG
Ca+2 2nd messenger
→ ↑ contractn
phosphorylatn of other proteins
→ cellular response
if M2, M4
G-protein
inhibitory G-protein
↓ adenylyl cyclase
↓ conversion of ATP to cAMP
↓ Ca+2 release
↓ contractility of cardiac muscle
كده إحنا عرفنا الـ muscarinic receptor بتشتغل بأي Mechanism
Phosphitidyl inositol diphosphate
وقبلها قلنا إن الـ Nicotinic receptors بتشتغل بالـ ion channel
يبقى كده إحنا خلصنا كل الـ Cholinergic receptors
تعالوا بقا نشوف الـ Adrinergic receptors بتشتغل بـ طريقة أي Mechanism
22
Cholinergic Receptors
miscarinic R
M1 M2 M3 M4 M5
PIP3
G protein
Nicotinic R
Ion channel

Molecular Basis of Adrenoreceptors Function

* all of Adrinergic receptors are G-Protein Coupled Receptors (GPCRs) where G-proteins is Linked to heterotrimeric Subunits (α, β, γ)

* G-proteins are signal transducers that convey information from the receptor to one or more effector molecules

و آخر حاجة هنشوف جدول مسلى جداً جداً عن الـ ؛
والحقيقة معرفش مدى اهميته بس
اعرفوا منه الحاجات المميزة زى
الـ heart والـ eye والـ GIT ،
كده يعني ٠٠٠٠٠

The Main Effects of ANS

Organ	Sympathatic effect	Adrenergic receptor type	Parasympathatic effect	Cholinergic receptor type.
1. Heart	Rate ↑	β_1	Rate ↓	M_2
2. Sinoatrial node	Force ↑	β_1	Force ↓	M_2
3. Atrioventricular node	Automaticity ↑	β_1	conduction velocity ↓	M_2
4. Ventricular muscle	"	β_1	arterioventricular block	M_2
5. Coronary artery	constriction, dilatation	$\alpha_1, \alpha_2, \beta_2$	vasodilatation	due to EDRF (NO) release in response to stimulation of non innervated M_3 receptors
6. Muscle	Dilatation	β_2	-	
7. Skin	constriction	α_1		
8. Brain	constriction	α_1		
9. Intestine	Constriction	α	dilatation	M_3 [NO]
10. Salivary gland	constriction	α	"	M_3
11. Vein	"	α	activation of NO synthase	M_3
12. GIT :				
a) Smooth muscle	motility ↓	α_2, β	Motility ↑	M_3
b) Sphincters	constriction	α_1	Relaxation	M_3
c) Glands	secretion ↓	α_2	Secretion ↑	M_3
			Gastric acid secretion ↑	M_1
13. Uterus :				
a) pregnant	contraction	α_1	variable	M_3
b) non pregnant	Relaxation	β_2		

14- Male sex organ	Ejaculation	α_1	erection	M_3
15- Eye:				
a) pupil	dilatation (contraction of radical muscle of iris) "mydriasis"	α_1	contraction of circular muscle causing constriction "miosis"	M_3
b) Ciliary muscle	relaxation (slight)	β_2	Contraction	M_3
16- Skin:				
a) Sweat gland	sec. (mainly cholinergic)	α_1	No effect	M
b) pilomotor	piloerection	α_1	No effect	—
c) sweat	secretion (thick)	α_1	secretion (watery)	M_3
17- liver	- glycogenolysis - gluconeogenesis	α_1, β_2	No effect	—
18- Adrenal medulla	Secretion of Adrenaline and nor Ad. [No sympathatic innervation]			N
19- Fat cells	Lipolysis	β_3	—	—
20- Urinary bl.:				
a) detrusor m.	relaxation	β_2	contraction	M_3
b) trigone & sphincter	contraction	α_1	relaxation	M_3

Pray 4 us a Lot oooo

* inhibits M_1 R → Pirenzepine
* 〃 Nn R → hexamethonium
* 〃 Nm R → d-tubocuranine
* Cholinomimitics → Ach - methacholine - Carbachol - Bethanec
  (methacholine, Bethanec → ↑ selective M R)
  → muscarine, pilocarpine
  Nicotine, Lobeline
* DMPP → Dimethyl, phenyl piperazine ≃ nicotine